KPNβ₁, also known as importin-β, is part of the karyopherin superfamily of nuclear transport proteins.¹ The classical importin-α/β system is believed to import up to half of the nuclear traffic.² Importins and exportins transport pro-oncogenic mediators across the nuclear membrane and are found to be overexpressed in a number of cancer types, including breast, colon, esophageal, gastric, lung, lymphoma, melanoma, pancreatic, and prostate cancer.³ The nuclear pore complex (NPC) is composed of approximately 30 proteins (nucleoporins) that are arranged octagonally around a central channel. KPNβ₁ participates in the classical nuclear import pathway alongside its adaptor protein – importin-α. Importin-α first recognizes and binds the cytoplasmic cargo via its nuclear localization signals, and then associates with importin-β via the importin-β binding (IBB) domain. This complex (nuclear localization signals–importin-α–importin-β) then traverses the nuclear pore complex.⁴ This active transport is able to occur against the concentration gradient, due to varying levels of Ran, a GTPase.⁵

KPNβ₁ has recently been shown to regulate proliferation of human glioma cells via the Wnt–β-catenin pathway.⁶ Glioblastoma multiforme is the most frequent brain cancer in adults and is highly infiltrative.⁶ Despite current treatments of neurosurgery and chemoradiotherapy, median survival remains around 14.6 months, and 5-year survival is <5%.⁷ Lu et al showed that the relative expression of KPNβ₁ correlated with the World Health Organization (WHO) grades of human glioma, with higher expression of KPNβ₁ correlating with more severe WHO glioma classification.⁸ Additionally, higher expression of KPNβ₁ correlated with lower 5-year survival ratio on Kaplan–Meier survival curves.⁹ Wnts are glycoproteins that are involved in cell proliferation, differentiation, and oncogenesis, and regulate β-catenin in their pathway.¹⁰ KPNβ₁ has recently been elucidated as a regulator of glioma-cell proliferation via the Wnt–β-catenin pathway.¹¹ Down-regulation of KPNβ₁ has been shown to inhibit glioma proliferation in vitro. Additionally, cells with lower levels of KPNβ₁ showed decreased nuclear β-catenin, demonstrating that KPNβ₁ played a role in the nuclear transport of β-catenin in the Wnt–β-catenin pathway.¹² KPNβ₁ has previously been shown to play a role in translocating β-catenin, which accelerates glioma proliferation.¹³

Another role of KPNβ₁ and glioma is the transport of GLI1 into the nucleus.¹⁴ GLI1 was discovered in human gliomata,¹⁴ and is a nuclear regulator of the Hedgehog (Hh)-signaling pathway.¹⁵ Dysregulation of this pathway leads to aggressive tumorigenesis. Hh normally binds to and inactivates Patched (Ptc). When Ptc is inhibited, Smoothened (Smo) is released and triggers a signaling cascade that ends in nuclear localization of GLI.¹⁶ SuFu is an additional negative regulatory protein that anchors GLI in the cytoplasm during inactivation of the Hh-signaling pathway.¹³ KPNβ₁ binds GLI1 with high affinity, and the GLI1-binding site on the N-terminus for SuFu overlaps with the GLI1-binding site for KPNβ₁. This results in competitive interaction.

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binding of GLI1 based on relative concentrations of KPNβ1 and SuFu.9 When KPNβ1 is bound to GLI1 (rather than SuFu bound to GLI1), GLI1 can undergo nuclear import and thereby play a role in tumorigenesis.9 Various studies have found different levels of GLI1 in malignant glioma. Zhu and Lo performed genome-wide copy-number analysis on 31 glioma samples and found that 22.6% of these samples had amplified GLI1.6 Therefore, inhibition of nuclear import of GLI1 via KPNβ1 has the potential to inhibit oncogenesis in glioma as a novel therapeutic strategy.6 Interestingly, KPNβ1 has also been indicated in the development of secondary brain tumors.9 Childhood acute lymphoblastic leukemia commonly results in treatment-related secondary brain tumors.9 This is due in part to cranial irradiation (and treatment with antimetabolites), though a genetic predisposition is also necessary.9 In a study by Edick et al., ~20% of patients developed secondary brain tumors, comprised of glioblastoma multiforme, anaplastic astrocytoma, primitive neuroectodermal tumors, and embryonal neuroepithelial tumors.9 Genetic analysis of pretreatment acute lymphoblastic leukemia blasts indicated the KPNβ1 gene, along with STAT4, NFIC, and HNRPL (all involved in tumor growth and trafficking), to have high significance in the development of secondary brain tumors.9 This supports the role of KPNβ1 in oncogenesis and cancer-cell viability and suggests its potential use as a predictive factor for secondary brain tumors. In conclusion, KPNβ1 is a promising target for anticancer therapeutics, including a potential for inhibition of certain neurological malignancies.

Disclosure

The authors declare no conflicts of interest in this work.

References